

formation of transmembrane pores [1]. Experimental methods, such as solid-state NMR, have shed light on the relative orientation of magainin 2 and PGLa on membranes with different lipid composition [2,3], but there is a general lack of information on the structure of the pore and the specific interactions that lead to its stabilization. In the present work, we studied the structure and dynamics of transmembrane pores formed by magainin 2 and magainin 2/PGLa (2:2) tetramers by all-atom molecular dynamics simulations performed at the Anton supercomputer (Pittsburgh Supercomputing Center). For both systems we observed stabilization of a pore. The 9- μ s simulation time allows a detailed analysis of its structure and properties, the role of the lipids surrounding it, and the relative orientation of magainin 2 and PGLa in the membrane.

References

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Modulation of the Interaction Between Detergent Micelles and Model Peptide Antibiotics by Varying the Peptide Charge Distribution

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With rising disease rates and decreasing effectiveness of conventional antibiotics, there is an immediate need for new antibiotics. One promising solution is through cationic antimicrobial peptides, which act by perturbing bacterial membranes. We are investigating model peptide antibiotics composed primarily of the hydrophobic dialkylated amino acid Aib (α -aminoisobutyric acid), which imparts a strong 3_{10} -helical bias due to steric hindrance at the α -carbon. Cationic lysine residues were placed in adjacent locations in the center of the helix (KK45) or one full turn apart (KK36). Micelles of dodecylphosphocholine (DPC) or sodium dodecyl sulfate (SDS) were used as zwitterionic or anionic membrane models, respectively. The interaction of model peptides with micelles can provide valuable information about the role of helical structure and peptide charge distribution on peptide-membrane interactions. Here we present thermodynamic and spectroscopic data characterizing the peptide-micelle interactions. Binding enthalpies for the interactions of KK36 and KK45 with DPC and SDS micelles were measured using isothermal titration calorimetry (ITC). Preliminary data suggests that binding to SDS micelles is exothermic, while binding to DPC micelles is endothermic. In both cases, KK45 has a more favorable binding enthalpy than KK36. Measurements of longitudinal relaxation times (T1) in the absence and presence of a gadolinium line broadening reagent indicate that KK45 is more buried than KK36 in SDS micelles, and that both peptides are more buried in SDS micelles than in DPC micelles. These results suggest that the enthalpy of binding is dominated by hydrophobic interactions between the Aib sidechains and the detergent molecules. These interactions are enhanced in KK45, possibly because the charges are more localized to the center of the helix.

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Isomeric Model Antibiotic Peptides Differing Only in Charge Placement Adopt Different Helical Conformations

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The efficacy of existing antibiotics is slowly declining as species of bacteria are evolving, increasing the need to find new antibiotics. One promising opportunity lies in peptide antibiotics, which are commonly helical and cationic. Our model antibiotic peptides are composed primarily of the hydrophobic dialkylated amino acid Aib (α -aminoisobutyric acid), which imparts a strong 3_{10} -helical bias due to steric hindrance at the α -carbon. Cationic lysine residues are substituted into strategic locations in the sequence. Previous studies have reported that substitution of monoalkylated amino acids into an Aib-rich sequence can impact helical shape. We report here the effect of charge placement on peptide helical structure in two solvents: DMSO (dimethyl sulfoxide), and water. We are focusing on two octameric peptides, in which two lysine residues are placed in adjacent locations in the sequence (KK45), or one turn apart (KK36). NMR data indicates that in DMSO, KK36 adopts a canonical 3_{10} -helical structure, while the KK45 helix is kinked. However, circular dichroism

spectra and NMR measurements of amide temperature coefficients for aqueous KK36 are not consistent with a canonical 3_{10} -helical conformation. We present here the complete titration of amide proton chemical shifts for KK36 and KK45 from aqueous (90:10 H₂O/D₂O) solution to DMSO-d₆ in order to identify the residues that are undergoing local environment changes as the bulk environment is changed. Measurements of the CD spectra of both peptides aqueous solution as a function of temperature will be correlated with the amide temperature coefficient data from NMR to obtain a more complete picture of solvent-induced conformational changes. Ultimately the correlation of structure and sequence will inform future antibiotic peptide design.

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Anisotropic Membrane Curvature Sensing by Antibacterial Peptides

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Some proteins and peptides have an intrinsic capacity to remodel lipid bilayers and sense membrane curvature via a curvature-dependent membrane binding energy. This is crucial for many biological processes. For example, antimicrobial peptides are believed to disrupt bacterial membranes by producing pores, which are highly curved structures. In this work, we explore a new computational method to investigate curvature sensing by simulating the interaction of single peptides with a buckled lipid bilayer, using the coarse-grained Martini model. We analyze three canonical antimicrobial peptides, magainin, melittin, and LL-37, and find qualitatively different sensing characteristics. In particular, melittin and LL-37 show anisotropic curvature sensitivity, but with different preferred orientations relative to the direction of greatest curvature. These findings provides new insights into the microscopic mechanisms of curvature sensing and its role in membrane remodeling, and should motivate experimental development to simultaneously measure position and orientation of membrane-bound proteins.

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Membrane Interaction of an Anti-Bacterial AApeptide Defined by EPR Spectroscopy

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Antibiotic resistance is one of the major threats to public health. AApeptides are a new class of synthetic anti-bacterial peptidomimetics that are not prone to antibiotic resistance, and are highly resistant to protease degradation. The broad-spectrum anti-bacterial activities of AApeptides are believed to be related to their unique structural features, which are capable of disrupting bacterial membranes selectively over human eukaryotic cells. How AApeptides selectively interact with bacterial membranes and alter lipid assembly and properties is unclear, but such information is essential in order to understand their antimicrobial activities. Here, by using electron paramagnetic resonance (EPR) techniques at 9 and 95 GHz, we have characterized the membrane interaction and destabilizing activities of an AApeptide, cyclic- γ -AApeptide, on liposomes mimicking bacterial and eukaryotic cell membranes. The analysis revealed specific interactions between cyclic- γ -AApeptides and negatively-charged lipid molecules. Subsequently, the AApeptide interacts strongly with the bacteria-mimic liposomes containing negatively-charged lipids, and thereby inhibits membrane fluidity. Furthermore, AApeptide binding induces significant lipid-lateral-ordering of the bacteria-mimic liposomes, detected by EPR at 95 GHz. In addition, AApeptide binding increases the membrane permeability of the bacteria-mimic liposomes. By contrast, minimal membrane fluidity and permeability changes were observed for liposomes mimicking eukaryotic cell membranes, consisting of neutral lipids and cholesterol, upon AApeptide binding. The results revealed that the intrinsic features of AApeptides are important for their ability to selectively disrupt bacterial membranes, the implications of which extend to developing new antibacterial biomaterials.

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Activity of Antimicrobial Peptide Protegrin-1 is Tuned by Membrane Cholesterol Content

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